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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/625,085

Applicant(s)

GRATZER ET AL.

Examiner

Michele K. Joike

Art Unit

1636

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 November 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,7-10,12,13 and 16-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,7-10,12,13 and 16-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1, 3, 4, 7-10, 12, 13 and 16-20 are pending and examined. Any rejection of record in the previous Office Action, mailed February 22, 2010 that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 4, 7-10, 12, 13, 16, 17, 19 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Keating et al in view of Brown et al, and in further view of Yang et al and Tanaka et al.

Response to Arguments Concerning Claim Rejections – 35 USC § 103(a)

Applicants' arguments filed on February 22, 2010 have been fully considered but have not been found persuasive. The following grounds of traversal are presented:

Applicants argue that Keating et al do not combine growth of the cells and production of a product produced by the activity of an enzyme (luciferase). Moreover,

Keating et al use mutant ATM promoters, which results in a dramatic reduction of luciferase activity. Therefore, Keating teaches away. The present inventors have discovered that by combining an assay based on growth with an assay based on conversion of a substrate, the signal-to-background ratio can be markedly improved, because the enzyme activity is measured after finishing growth. The necessity for separating growth and measurement of enzyme activity is not obvious from Keating.

Brown et al has not realized that separating the addition of the test compound and substrate would increase the signal-to-background ratio. Therefore, one of skill in the art would not be motivated to alter Brown's assay.

Brown et al teach that CPRG is cell permeable, and applying Tanaka on Brown would mean that one of skill in the art would apply digitonin to increase cell permeability in order to increase uptake of CPRG. However, the present inventors separated addition of the substrate and test compound, which also addressed the problem that CPRG is inhibited during ligand-induced growth.

There would be no incentive to use Yang since the dual reporter assay uses two fluorescent proteins. Using different fluorophores is only suitable to detect different proteins or different localizations.

Applicant's arguments have not been found persuasive for the following reasons.

Applicants are claiming that the target molecule affects cellular propagation. Keating et al teach a molecule (ATM) that is known to be involved in cell cycle control. Modulating the activity of ATM induces luciferase activity, so growth of cells is combined

with the activity of luciferase. Keating et al also uses non-mutated ATM promoters used in assays with luciferase (p.4285). Therefore, there is no teaching away. Keating separates growth and measurement of enzyme activity because there is a time delay when adding the substrate for luciferase. Applicants are only claiming a delay. There is no time period specified for the delay, and Applicants are not claiming that the enzyme activity is measured after finishing growth.

In response to applicant's argument that Brown et al has not realized that separating the addition of the test compound and substrate would increase the signal-to-background ratio, and therefore, one of skill in the art would not be motivated to alter Brown's assay, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Brown et al recognize the benefit of using two different reporters, even if they do not realize that use of the two different reporters will improve the signal-to background ratio. Keating teaches adding the substrate after a delay, and Brown teaches using a growth marker and an enzymatic marker. Applicants have taught this is what is required for an improved signal-to background ratio. Therefore, it would be inherent that combining the methods of Keating and Brown would also cause an improved signal-to background ratio.

Even if CPRG is inhibited during ligand growth, the fact that is present at all times will mean that it is readily available when needed. Also, just because it is inhibited does not mean it is not being converted. It may not be the most efficient, but the assay on

Brown performed as needed. Additionally, permeabilizing the membrane will allow for more CPRG to be available, even if CPRG is cell permeable.

Yang is merely present to reinforce that using two reporters instead of one is beneficial. Even though they use two fluorophores, they teach that optimizing the reporters used enhances expression levels. Brown teaches the use of a growth marker and an enzymatic reporter.

Response to Arguments Concerning Claim Rejections – 35 USC § 103(a)

Applicant's arguments, see page 11, filed February 22, 2010, with respect to the rejection(s) of claim(s) 18 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Brown et al.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Crossin et al in view of Keating et al, in view of Brown et al and in further view of US 20050118690 and Tanaka et al.

Crossin et al (PNAS 94: 2687-2692, 1997, specifically Abstract, Introduction, last paragraph, Exptl. Procedures, 2nd, 7th and last paragraph and Figure 4) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a target molecule, wherein an agonist, N-CAM, modulates a target molecule, GRE, which induces a luciferase reporter. N-CAM inhibits cell proliferation. In measuring luciferase activity, cells were lysed. They also teach a second cell with a

second target molecule, CM-V and a second reporter beta-galactosidase. N-CAM is the agonist. However, Crossin et al do not teach the use of two reporters, using the same promoter for each reporter, or adding the substrate after a delay.

Keating et al (Oncogene 20: 4281-4290, 2001, specifically Introduction, p. 4282 and Materials & Methods, 1st and 6th paragraphs) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a target molecule, wherein an agent, EGF, modulates a target molecule, ATM (a heterologous kinase), which induces a luciferase reporter. ATM is known to be involved in cell cycle control (see Abstract & Introduction). Cells were incubated with EGF for 16 hours before cells extracts were prepared. EGF was added during log phase, therefore at least one or two cell cycles have occurred. Firefly luciferase substrate (LARII) was added and reporter activity was measured using a Dual Luciferase Assay. However, Keating et al do not teach the use of two different reporters, or using the same promoter for each reporter.

Brown et al (Yeast 16: 11-22, 2000, specifically, pp. 12-14, 16, 19 and Table 3) teach a dual reporter assay for evaluating chimeric yeast/mammalian Gα proteins in *S. cerevisiae*. Gα proteins can modulate effectors to cause signal propagation. GPCRs can also directly affect propagation. Table 3 lists the different concentrations of agonists used to determine the effect on the pheromone response pathway. The two reporter constructs used are FUS1-HIS3 and FUS1-lacZ. As stated in the specification on page 10, when these two constructs are combined, the improved signal-to-background ratio is 100-150:1. The same promoter allows for equivalent regulation. A

beta-galactosidase assay is performed with CPRG as the substrate to measure activity. CPRG is converted to chlorophenol red after 24 hrs. of incubation. Cell growth is also determined. The cells were also disrupted to perform a Western blot. Glass beads are used to disrupt the membrane. However, they do not teach adding a substance capable of permeabilizing a membrane.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teaches that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP).

Tanaka et al (Annals of Thoracic Surgery, 72: 1173-1178, 2001, especially p. 1173) teach adding digitonin, a detergent, was added together with the substrate, cisplatin, to cells. Digitonin permeabilizes the cell's membrane. One would be motivated to use Tanaka et al because they teach that digitonin increases cellular permeability and enhances intracellular uptake.

The ordinary skilled artisan, desiring to use a dual reporter system, would have been motivated to combine the teachings of Crossin et al with the teachings of Keating et al, Brown et al, US 2005/0118690, and Tanaka et al because using two different

types of markers allows for different types of expression, growth of cells in media supplemented with a substrate, and detection of expression based on enzymatic activity. This is beneficial because it allows for the isolation of such transformants though selective pressures. It would have been obvious to one of ordinary skill in the art to use dual reporters because US 2005/0118690 teaches that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells, and the other reporter gene provides a colorimetric marker. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicants argue that Crossin does not teach the use of two cells, but teaches that the vectors are transformed into one cell. However, Crossin uses the plural "cells" throughout the reference, including the materials and methods section discussing regarding transformation. While the number of cells is not specified, there is no reason to believe it is only one cell. Additionally, US 2005/0118690 does not teach that the substrate should be applied after contacting the cell with the candidate compound. However, Keating et al teach this step.

Allowable Subject Matter

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on (571)272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Primary Examiner, Art Unit 1636

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